efficient drug delivery systems, which by their very design enable people to readily develop and sustain nicotine addiction."[305]

FDA agrees with these independent scientific bodies.

2. The tobacco industry takes issue with FDA's citations of studies to show that certain levels of nicotine cause pharmacological effects.

The tobacco industry argues that three studies cited by FDA to estimate the minimum pharmacological dose of nicotine do not show that tobacco products cause significant pharmacological effects. The industry also contends that two studies cited by FDA to show that smokers can control their nicotine intake do not reflect common tobacco consumption behavior.

The industry mischaracterizes FDA's reasons for citing the studies. FDA did not cite animal research and a study on the nicotine nasal spray to prove that cigarettes cause pharmacological effects in humans. Rather, the studies were cited to demonstrate that a very low blood level of nicotine that is easily attainable with cigarettes produces pharmacological effects across species. This observation complements overwhelming evidence from clinical, epidemiological, and laboratory studies showing that cigarettes and smokeless tobacco cause significant pharmacological effects in humans.

Similarly, FDA did not cite studies on the extremes of nicotine intake to demonstrate exactly how much nicotine every smoker obtains. Rather, the studies were cited to demonstrate that nicotine intake from cigarettes has the potential to vary widely across a range of levels that produce significant pharmacological effects in humans.

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[305] American Psychological Association, Comment (Dec. 28, 1995), at 2 (emphasis added). *See* AR (Vol. 531 Ref. 123).

FDA also notes that the industry offers no data contradicting FDA's studies. The industry also fails to contest other sources cited by FDA—including some from the tobacco industry—that clearly support the conclusion that nicotine levels in commercial tobacco products produce significant pharmacological effects in consumers. *See* Jurisdictional Analysis, 60 FR 41571–41572, 41632–41640.

Finally, FDA notes that the industry misinterprets a study by Perkins *et al.*[306] on nicotine nasal spray. *See* section II.A.7.d., above.

3. The industry contends that nicotine doses provided by cigarettes produce only a "minimal response in laboratory animals and a small number of human subjects" and that, therefore, FDA has not established that nicotine doses delivered by cigarettes produce substantial pharmacological effects.

FDA disagrees. Many studies demonstrate such significant effects as systemic cardiovascular reactions in nontolerant humans and animals,[307] sickness produced by a single tobacco exposure in nontolerant individuals,[308] and changes in brain electrical activity comparable to those produced by other addictive drugs.[309] As described in sections II.A.4., above, and II.B.2., below, use of tobacco also produces significant effects on attention, mood, cognition, and weight regulation. These are not minimal effects.

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[306] Perkins K, Grobe J, Scierka A, *et al.*, Discriminative stimulus effects of nicotine in smokers, in *International Symposium on Nicotine: The Effects of Nicotine on Biological Systems II*, eds. Clarke PBS, Quik M, Thurau K, Adlkofer F (Basel: Birkhauser Verlag, 1994), at 111. *See* AR (Vol. 42 Ref. 111).

[307] Surgeon General's Report, 1988, at 47. *See* AR (Vol. 129 Ref. 1592).

[308] *Id.* at 594.

[309] Pritchard WS, Electroencephalographic effects of cigarette smoking, *Psychopharmacology* 1991;104:485-490, at 485, 488. *See* AR (Vol. 105 Ref. 965).

II.A.7.

Nicotine's capacity to produce and sustain addiction, as described in section II.A.2., above, is another example of a significant pharmacological effect.

Because the vast majority of chronic smokers are highly tolerant to nicotine, not all of the pharmacological effects of nicotine are evident with every cigarette and pinch of smokeless tobacco. As described in section II.A.3.c.i., above, the severe degree of tolerance produced by nicotine seems to greatly exceed that produced by cocaine and to be more comparable to that produced by morphine in the reduction of responsiveness to acute doses after a period of repeated exposure.

4. The tobacco industry argues that there is no "addictive level" of nicotine. This contention is partly based on the claim that nicotine intake is not well correlated with quitting success. The industry also argues that FDA's Drug Abuse Advisory Committee did not identify a threshold addictive dose of nicotine. Without such an "addictive level," the industry concludes, the nicotine in tobacco products cannot have a substantial pharmacological effect.

FDA disagrees. The tobacco industry misinterprets the scientific literature on cessation studies, the actual conclusion reached by the Committee, and the concept of "addictive level."

A large body of literature has shown that nicotine dependence level is among the strongest general predictors of withdrawal severity and duration of abstinence. *See* section II.A.7.f., above.[310] These data support the conclusion that the relationship between level of drug intake and dependence level is similar to that observed with other

[310] Surgeon General's Report, 1988, at 315-321, 522-523. *See* AR (Vol. 129 Ref. 1592).

forms of drug addiction, namely that level of drug intake is generally but not precisely correlated positively with dependence level and that there is wide individual variability.[311] It is because drug intake alone is not a perfect measure of dependence that diagnostic instruments such as the DSM are necessary for clinical practice.

The industry also misrepresents the findings of the FDA Committee, which concluded that all currently marketed cigarettes contain an addictive dose of nicotine, but that the data were not sufficient to determine a threshold dose below which the product would *not* pose a risk of addiction.[312] The main concern of the Committee was that, in attempting to set a lower limit, any error on the high side would permit the industry to market products that would be addictive to some persons. The Committee was particularly concerned that persons who have not developed tolerance to nicotine, such as children, might find even the doses posed by Benowitz and Henningfield (approximately one-tenth of the delivery of a typical cigarette) to be addictive.[313]

FDA concurs with the Committee that all currently marketed cigarettes contain addictive levels of nicotine.

5. The tobacco industry argues that any compensation occurring in response to cigarettes with lower yields of tar and nicotine is limited and of short duration. Thus, according to the industry, smokers of low-yield cigarettes do not obtain pharmacologically active doses of nicotine. The industry contends that this proposition is supported by an

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[311] *Id.* at 315-321.

[312] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 346-353. *See* AR (Vol. 255 Ref. 3445).

[313] *Id.* at 346-353.

article by Benowitz and Henningfield.[314] The industry also argues that smokers actually compensate for changes in tar delivery rather than nicotine delivery. Furthermore, it denies that cigarette vent-hole blocking is a significant means of compensation. The industry thus argues that compensation for nicotine does not occur.

FDA disagrees. Tobacco industry research demonstrates that smokers significantly compensate for nicotine. For example, research presented at a tobacco industry conference in 1974 demonstrated that, "whatever the characteristics of cigarettes as determined by smoking machines, the smoker adjusts his pattern to deliver his own nicotine requirements." *See* Jurisdictional Analysis, 60 FR 41663. Other examples of the tobacco industry's understanding of compensation are documented in the Jurisdictional Analysis. *See* 60 FR 41572–41575.

Furthermore, FDA cited research in the Jurisdictional Analysis demonstrating that the actual amount of nicotine delivered to the smoker does not correlate with the machine-measured yield of the cigarette and that smokers who smoke "low-yield" cigarettes have been shown to obtain substantially more nicotine than the advertised yield. *See* 60 FR 41659-41665. In one study, for example, the advertised yield of tested cigarettes ranged from 0.1 to 1.6 mg of nicotine, but the actual nicotine intake by the smokers asked to smoke these cigarettes ranged from 0.75 to 1.25 mg.[315] Other studies have also found that the nicotine levels measured in smokers' blood bear either no relationship or a minimal

[314] Benowitz NL, Henningfield JE, Establishing a nicotine threshold for addiction, *New England Journal of Medicine* 1994;331:123-125. *See* AR (Vol. 28 Ref. 218).

[315] Gori GB, Lynch CJ, Analytical cigarette yields as predictors of smoke bioavailablity, *Regulatory Toxicology and Pharmacology* 1985;5:314-326. *See* AR (Vol. 12 Ref. 142).

relationship to the nicotine yield of the cigarettes being smoked and that machine-measured yields of low-tar/low-nicotine cigarettes significantly underestimate true rates of nicotine absorption. In most of these studies, the subjects were people who were smoking their usual brand of cigarettes and showed levels of nicotine not related to Federal Trade Commission (FTC) yields, thus refuting the suggestion that compensation is short-lived.[316]

The tobacco industry misrepresents the position of Benowitz and Henningfield on compensation. These authors have repeatedly published research demonstrating that smokers compensate with current cigarettes by smoking harder or by blocking the vent holes.[317]

In the Benowitz and Henningfield paper cited by the tobacco industry, the authors were discussing cigarettes—not currently on the market—with so little available nicotine that it would be impossible to compensate for reduced nicotine except by smoking an impractical number of cigarettes. The total nicotine content of these cigarettes would have been only about 5% of the content of currently marketed cigarettes and would have permitted a maximum delivery of only about 10% that of current cigarettes. The authors predicted that few smokers would permanently smoke the 200 or more cigarettes needed to obtain the nicotine intake typically delivered by 20 conventional cigarettes. Thus, Benowitz and Henningfield believed that, if denied access to regular nicotine cigarettes, smokers would either quit or adjust over time to substantially reduced nicotine intake.

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[316] Surgeon General's Report, 1988, at 158-159. *See* AR (Vol. 129 Ref. 1592).

[317] *Id.* at 158-163.

Henningfield JE, Kozlowski LT, Benowitz NL, A proposal to develop meaningful labeling for cigarettes, *Journal of the American Medical Association* 1994;272:312-314. *See* AR (Vol. 313 Ref. 4846).

This prediction is entirely inapplicable to currently marketed "low-yield" cigarettes delivering 0.1 mg of nicotine as measured by the smoking machine; a smoker need smoke only about 30 of these to obtain the amount of nicotine obtained with 20 "full flavor" cigarettes.[318]

The tobacco industry's denial that vent blocking occurs misses important points of FDA's position on this issue. FDA has simply posed vent blocking as the most likely explanation for the well-documented fact that there is almost no difference in the nicotine levels observed in the bodies of smokers who smoke brands with widely varying FTC yields. Smoking more cigarettes is only one means by which smokers compensate. Vent blocking is another means at the smoker's disposal to compensate. Indeed, the studies relied on by the tobacco industry suggest that the frequency of vent blocking is inversely proportional to the yield of the cigarette. In other words, the lower the tar and nicotine yield of the cigarette, the more the smoker blocks the vent holes. These data support the position that vent blocking plays an important role in compensation. There are, in addition, other compensation mechanisms, such as smoking more of the cigarette than is smoked in testing machines, smoking more aggressively, and taking deeper inhalations.[319]

The tobacco industry contends that smokers may compensate for tar rather than for nicotine. This contention is contradicted by a very extensive body of literature, documented in detail in the 1988 Surgeon General's Report,[320] showing that, when the

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[318] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 106. *See* AR (Vol. 255 Ref. 3445).

[319] Surgeon General's Report, 1988, at 153-158. *See* AR (Vol. 129 Ref. 1592).

[320] *Id.* at 153-169, 282-283.

level of nicotine in cigarettes is manipulated, smokers alter their smoke intake. Although the relationship is not perfect, it is similar to that which has been observed with other addictive drugs in numerous animal studies and some human studies. That is, when the dose of the drug in the cigarette is increased, the number of unit doses that are self-administered decreases generally, although not proportionally. This results in the frequent observation of increased overall drug intake.[321]

Conversely, when the dose is decreased, the number of unit doses that are self-administered generally increases, although usually not proportionally. The relationship has been demonstrated with respect to cigarette smoking by: (1) administering nicotine to smokers via other routes, which results in decreased smoking; and (2) administering the nicotine blocker mecamylamine to smokers (which reduces the effects of nicotine on receptors in the brain), resulting in increased smoking.[322] A study on compensation for smokeless tobacco cited by the smokeless tobacco industry showed that users increased their consumption when switched to a low-nicotine product.[323]

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[321] *Id.* at 282-283.

[322] *Id.* at 165-169.

[323] Andersson G, Axell T, Curvall M, Reduction in nicotine intake and oral mucosal changes among users of Swedish oral moist snuff after switching to a low-nicotine product, *Journal of Oral Pathology & Medicine* 1995;24:244-250. *See* AR (Vol. 526 Ref. 95, vol. VII).

The low-nicotine product had a lower pH than the higher-nicotine product. Because lower pH reduces absorption *see* section II.D., below, measurements of nicotine intake cited by the industry do not accurately reflect compensation in this study.

B. CONSUMERS USE CIGARETTES AND SMOKELESS TOBACCO TO OBTAIN THE PHARMACOLOGICAL EFFECTS OF NICOTINE AND TO SATISFY THEIR ADDICTION

In section II.A., above, the Agency concludes that the foreseeable pharmacological uses of cigarettes and smokeless tobacco establish that tobacco manufacturers intend their products to affect the structure and function of the body. The Agency may find additional evidence of such intent through evidence that consumers commonly use tobacco products for pharmacological effects. Where consumers use a product predominantly or nearly exclusively to obtain any of the effects on the structure or function of the body produced by a substance, such evidence would alone be sufficient to establish manufacturer intent. *See ASH v. Harris,* 655 F.2d 239-240.

The Agency made extensive findings regarding consumer use of tobacco products in the Jurisdictional Analysis. *See* 60 FR 41576-41581. FDA received comments from the tobacco industry, public health and medical organizations and practitioners, and other members of the public. Upon review of the evidence in the administrative record and careful analysis of the comments on the Jurisdictional Analysis, the Agency concludes that the evidence demonstrates that consumer use of cigarettes and smokeless tobacco for the pharmacological effects of nicotine is predominant, in fact nearly exclusive. Moreover, the Agency finds that other factors associated with tobacco use—including taste and habit—are significant to almost all consumers only by their association with nicotine's pharmacological effects on the brain. Thus, FDA finds that actual consumer use of cigarettes and smokeless tobacco for the pharmacological effects of nicotine provides an

independent basis for the conclusion that these products are intended to affect the structure and function of the human body.[324]

In section II.B.1., below, FDA discusses its authority to consider evidence of consumer use in establishing intended use. FDA presents its major findings and responds to significant comments in sections II.B.2. and 3., below. In section II.B.4., below, FDA responds to all other substantive comments.

1. "Intended Use" May Be Established on the Basis of Actual Consumer Use

The legislative history of the Act clearly states that consumer use can be probative of a product's intended use. For example, the House Report on the Medical Device Amendments of 1976 states that "*[t]he Secretary may consider . . . use of a product in determining whether or not it is a device.*" H.R. Rep. 853, 94th Cong., 2d Sess. 14 (1976) (emphasis added), *reprinted in* An Analytical Legislative History of the Medical Device Amendments of 1976, Appendix III (Daniel F. O'Keefe, Jr. & Robert A. Spiegel, eds. 1976). Similarly, the legislative history of the 1938 Act states expressly that "the *use* to which the product is to be put *will determine the category into which it will fall.*" S. Rep. No. 361, 74th Cong., 1st Sess. 4 (1935) (emphasis added), *reprinted in* 3 Legislative History 660, 663.

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[324] In this case, there is evidence not only of actual consumer use, but other evidence of manufacturer intent, including: (1) evidence that nicotine's addictive properties and other pharmacological effects are foreseeable to a reasonable tobacco manufacturer; and (2) evidence from the statements, research, and actions of manufacturers establishing that they intend their products to affect the structure or function of the bodies of tobacco users. *See* sections II.A., C., and D. Thus, although the evidence establishes that consumers use cigarettes and smokeless tobacco predominantly or nearly exclusively for the pharmacological effects of nicotine, this finding is not necessary to permit reliance on the evidence of actual consumer use. Relied on in conjunction with the other evidence of manufacturer intent, evidence of actual consumer use provides substantial additional support for the Agency's conclusion.